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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,527	11/28/2003	Cedric Francois	LOU02-016-US	8907

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EXAMINER	
CHANDRA, GYAN	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,527	FRANCOIS, CEDRIC	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 24-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/14/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III, claims 20-23 in the reply filed on 02/18/2005 is acknowledged. The traversal is on the ground(s) that claims 24-26 and 27-31 should be considered to group them with Group III as they read on the elected species of Group IV. Applicant argues that restriction is proper of the identified groups are independent or distinct and should have undue search burden. The groups mailed in restriction requirement on 1/12/2005 under US 121 and 372, would still be the same as applied in the US restriction practice 35 U.S.C. 121. Group III is drawn to a vesicle comprising a phospholipid and a T-cell apoptosis inducing agent, classified in class 424, subclass 450. Group II is drawn to a method of treating a transplant comprising administering a phospholipid and a T-cell apoptosis inducing agent, classified in class 424, subclass 9.1. Because each group 1-7 of the previous office action are different and support separate inventions, restriction is proper. Furthermore, MPEP § 803 provides that the separate classification (i.e., class and subclass) of distinct inventions is sufficient to establish a prima facie case that the search and examination of the plural inventions would impose a serious burden upon the Examiner.

Searches for a method of treating a transplant comprising a T cell apoptosis inducing agent and a phospholipid (group 1), a method of treating a transplant comprising administering a vesicle comprising a phospholipids, at least one member selected from the group consisting of another polar lipid, a raft former and a fusion

protein, and a lipid (group 2), a vesicle comprising a phospholipid and a T cell apoptosis-inducing molecule (group 3), a vesicle comprising a phospholipid, a T cell apoptosis-inducing molecule and a polar lipid (group 4), a transplant contacted with a vesicle (group 5), a method of transplanting a transplant (group 6) and a method of treating a transplant comprising administering a T cell-apoptosis-inducing molecule, and a vesicle comprising a means for binding the T-cell-apoptosis-inducing molecule and a phospholipid where the vesicle has a fusion rate of 20 vesicle fusions/second (group 7) are not coextensive. Therefore, this creates an undue burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Status of Application, Amendments, And/Or Claims

Claims 1-39 are pending. Claims 1-19, and 24-39 are withdrawn from further consideration as being drawn to a nonelected Invention.

Claims 20-23 are examined on the merit to the extent that they read on the elected invention.

Information Disclosure Statement

The information disclosure statement filed 12/14/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all

other information or that portion which caused it to be listed. It has been placed in the application file, but the crossed references therein have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a vesicle comprising phospholipids and a T-cell apoptosis-inducing molecule. The narrower claims require that the apoptosis-inducing molecule be a lipid, which may contain a biotin. Thus the claims are drawn to a genus of lipid moieties and biotinylated lipids.

To provide undisclosed possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics for the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the chemical product, or any combination thereof. In this case, the only factor

present in the claim is either a lipid or a biotin moiety that comprises a T-cell apoptosis-inducing molecule. The claimed invention encompasses innumerable number of lipids and/or biotinylated lipids. In the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is *whatever is now claimed* (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).
Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vesicle comprising a known T-cell apoptosis

inducing molecule, does not reasonably provide enablement for any lipid or a biotin as a T-cell apoptosis inducing molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to which the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among

the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The Nature of the Invention: The claimed invention is drawn to a vesicle comprising (a) a phospholipid, and (b) a T-cell-apoptosis inducing molecule where the T-cell apoptosis-inducing molecule comprises (i) a lipid moiety and (ii) a biotin moiety.

The state of the prior art and the predictability or lack thereof in the art:
A complex signaling is involved in inducing apoptosis which is a natural mechanism of cell death. Gajate et al teach that an intracellular triggering of FAS pathway is a new mechanism of induction of apoptosis (Int. J. Cancer 85: 674-682, 2000). They used an antitumor ether lipid (ET-I8-OCH3) to induce apoptosis in a cell based assay using Jurkat cell. It is not clear that there are natural lipids, if any, can induce apoptosis which can be targeted as anti-tumor agent. The specification does not disclose any example with a lipid or a biotinylated lipid that is able to induce apoptosis and can treat a tumor in vivo. There is no guidance to how well a lipid or a biotin moiety can be used in a vesicle to induce T-cell apoptosis for the treatment of tumor to which claims are drawn. There is no working example of using a biotin moiety or a lipid to induce T-cell apoptosis in vivo

for the treatment of a tumor. It is unpredictable to use a biotin moiety or a lipid to induce T-cell apoptosis in vivo for the treatment of a tumor.

The amount of direction and guidance present and the presence or absence of working examples: Given the teachings of unpredictability found in the art, detailed teachings are required to be present in the disclosure in order to enable the skilled artisan to practice the invention commensurate in scope with the claims. These teachings are absent. Applicants generated a vesicle comprising a biotinylated phospholipid molecule which may induce Fas pathway to induce apoptosis (Example 7). But it is not clear how a fusogenic vesicle comprising a lipid or biotin moiety would treat tumor. It will require to a large number of experimentation to see any such effect, in any patient.

The breadth of the claims and the quantity of experimentation needed: Because the claims encompass a vesicle comprising (a) a phospholipid, and (b) a T-cell-apoptosis inducing molecule where the T-cell apoptosis-inducing molecule comprises (i) a lipid moiety and (ii) a biotin moiety, in the light of the teachings of the unpredictability found in the art discussed and because of the supra lack of sufficient teachings in applicants disclosure to overcome those teachings, it would require undue experimentation by one of skill in the art to be able to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 20 is rejected under 35 U.S.C. 102(b) as being anticipated by Kelley et al (U.S. Patent No. 5,919,643).

Claim is drawn to a vesicle comprising phospholipids, which is a stable vesicle former, and a T-cell-apoptosis inducing molecule.

Kelley et al teach that IFN beta production renders circulating T-cells to apoptosis by upregulating the cascade of metabolic events leading to programmed cell death (column 54, lines 40-44). They also teach that liposomes are vesiclular structures characterized by phospholipid bilayer membrane and an inner aqueous medium (column 31, lines 54-57). They teach that liposome can be used for delivering molecules to tissue specific site (column 31, lines 66-67 through column 32, lines 1-3).

Claim 20 is rejected under 35 U.S.C. 102(b) as being anticipated by Wiley (U.S. Patent No. 6,207,642).

Wiley teaches that liposomes or fusogenic lipid vesicles can be used for delivering gene or compound directly to target such as nucleus (column 27 lines 38-58). Liposomes are generally derived from phospholipids or other lipid substances (column

31, lines 33-35). Wiley teaches that programmed cell death (apoptosis) is a fundamental biological process and cells are induced to self-destruction through appropriate signals. T-cells that recognize self-epitopes are destroyed by apoptosis during maturation of T cell in the thymus and state that TNF related endothelium proliferative agents (TREPA) can be administered alone or with other apoptosis inducing agent to induce T cell mediated apoptosis (column 8, lines 56-67 through column 9, lines 1-14).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly et al or Wiley in view of Gajate et al (Int. J. Cancer 85: 674-682, 2000).

The claimed invention is drawn to a vesicle comprising (a) a phospholipid, and (b) a T-cell-apoptosis inducing molecule where the T-cell apoptosis-inducing molecule is a lipid.

The teachings of Kelly et al or Wiley are summarized as set forth supra. Neither Kelly nor Wiley teaches a lipid as a T-cell apoptosis inducing agent. Gajate et al teach a synthetic lipid ET-18-OCH3 that induces apoptosis through Fas pathway. They teach that normal cells are resistant to ether lipid whereas tumor cells are more permeable for the lipid (page 680, 1st paragraph of right side column). They also teach that the

leukemic cells are more sensitive to ether lipid than peripheral blood T lymphocyte (page 681, left column).

It would have been prima facie obvious to one of ordinary skill in the art to deliver an apoptosis inducing molecule as taught by Kelly or Wiley using a lipid for T-cell apoptosis activation as taught by Gajate et al. One of ordinary skill of the art would be motivated to use a T-cell apoptosis inducing molecule lipid with a reasonable level of success because Gajate et al show that ether lipids work through Fas pathway in activating apoptosis.

Claims 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelley et al or Wiley in view of Gajate et al as applied to claims 20-21 above, and further in view of Eve-Isabelle et al (Biochemistry 36: 3773-3781, 1997) or Walker et al (Nature 387:61-64. 1997).

The claimed invention is drawn to a vesicle comprising (a) a phospholipid, and (b) a T-cell-apoptosis inducing molecule where the T-cell apoptosis-inducing molecule comprises (i) a lipid moiety, (ii) a biotin moiety and (iii) N-(biotinoyl)-1,2-dihexadeanoyol-sn-glycero-3-phosphoethanolamine.

The teachings of Kelly et al or Wiley in combination of Gajate et al are summarized as set forth supra. Neither Kelly nor Wiley in combination with Gajate teach a biotinylated-lipid for using in a vesicle. Eve-Isabelle et al teach use of biotinylated-lipid to make fusogenic vesicle. They teach advantage of having biotin attached to lipid in

making vesicle fusogenic for delivering drugs or anchored proteins (page 3776, last paragraph of the left column through 3rd paragraph of the right side column, page 3780, 2nd paragraph of the right side column, page 3781, last paragraph of the left column). They used commercially available N-(biotinoyl)-1,2-dihexadeanoyol-sn-glycero-3-phosphoethanolamine biotinoyl phospholipid from Molecular Probes Company to synthesize vesicle. Walker et al also teach that vesicles of lipid bilayer have been used as a drug-delivery vehicle for many years. They teach making bilayer vesicles from biotinylated-lipid (page 61, abstract, page 62 1st paragraph of right side column). This meets all the limitations of the claimed invention.

It would have been prima facie obvious to one of ordinary skill in the art to deliver an apoptosis inducing molecule as taught by Kelly or Wiley in combination with Gajate using a biotinylated lipid to make a fusogenic vesicle as taught by Eve-Isabelle or Walker et al. One of ordinary skill of the art would be motivated to use a commercially available biotinylated lipid such as such as N-(biotinoyl)-1,2-dihexadeanoyol-sn-glycero-3-phosphoethanolamine as taught by EVe-Isabelle to make a fusogenic vesicle and would have added to this a lipid moiety comprising T-cell apoptosis inducing as taught by Gajate with a reasonable level of success.

Conclusion

No claim is allowed.

Art of Interest:

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Thomas et al. U.S. Publication 2004/0131587 (7/08/2004). Discloses an improved method for treatment of a tumor comprising administering a combination of two to five agents that cause apoptosis and/or necrosis of tumor cells.

2. Molecular Probes products: teaches N-(biotinoyl)-1,2-dihexadeanoyol-sn-glycero-3-phosphoethanolamine.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gyan Chandra
AU 1646
21 April 2005

JANET ANDRES
PRIMARY EXAMINER